Award Number: W81XWH-14-2-0193

TITLE: Prevention of Bone Loss after Acute SCI by Zoledronic Acid: Durability, Effect on Bone Strength, and Use of Biomarkers to Guide Therapy

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REPORT DATE: October 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
October 2016	Annual	29 Sep 2015-28 Sep 2016

4. TITLE AND SUBTITLE

Prevention of Bone Loss after Acute SCI by Zoledronic Acid: Durability, Effect on Bone Strength, and Use of Biomarkers to Guide Therapy

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-2-0193

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Thomas J. Schnitzer, MD, PhD

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Northwestern University, 633 Clark St., Evanston,IL 60208-0001

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
US Army Medical Research and Materiel Command
Fort Detrick, MD 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Rapid bone loss is a universal accompaniment of acute spinal cord injury (SCI) and leads to severe loss of bone mass and bone strength with a marked increased risk of fracture. This 24 month double-blind, randomized, placebo-controlled study evaluates in 60 participants the efficacy (bone mass and bone strength) and safety of zoledronic acid administered early after acute SCI to prevent bone loss, the duration of its effects and the value of using biomarkers to guide therapy. Data collection (bone imaging and biomarkers) occurs at baseline and after 3, 6 and 12 months during the first year; participants are re-randomized after 12 months with subsequent data collection at 18 and 24 months. Currently, all regulatory requirements for the study have been completed. Thirty (30) participants have been randomized and treated. No unexpected safety events have occurred. Data collection is on-going and additional patients are being screened for study entry.

15. SUBJECT TERMS
Spinal cord injury, bone mass, bone strength, osteoporosis, zoledronic acid

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
					USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE	UU	6	19b. TELEPHONE NUMBER *(include area code)*
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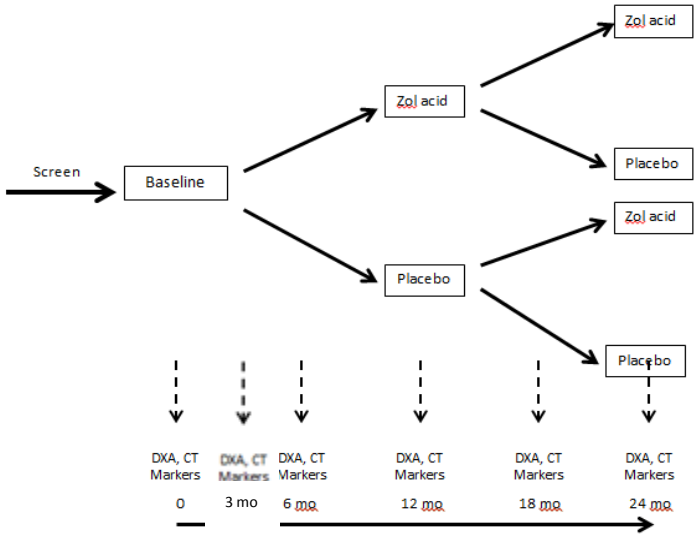
INTRODUCTION:

Rapid bone loss is a universal accompaniment of acute spinal cord injury (SCI) and leads to severe loss of bone mass and bone strength with a marked increased risk of fracture. The study proposed is a 2 year, randomized, double-blind placebo-controlled study of zoledronic acid to evaluate its efficacy and safety for the prevention of bone loss and maintenance of bone strength in individuals with recent onset SCI (see diagram below). At the end of the first year of the study, each treatment groups will be re-randomized to either zoledronic acid or placebo to evaluate the durability of response to zoledronic acid and the utility of serum bone markers to guide therapeutic decision making. DXA imaging, CT imaging and bone markers will be obtained at baseline, 3 months, 6 months, 12 months, 18 months and 24 months.



KEYWORDS: spinal cord injury, bone mass, bone strength, osteoporosis, zoledronic acid

OVERALL PROJECT SUMMARY:

All objectives outlined in the Statement of Work to be completed during the second year have been completed. All regulatory approvals have been maintained. Screening, enrollment and treatment of participants (Specific Aim 1, Major Task 3) continues, with 30 participants currently randomized and active in the study. Data are being obtained and entered into the study database, and study materials are being collected and maintained for future assay (biomarkers; part of Specific Aim 2, Major Task 1) or for image analysis (CT bone scans; part of Specific Aim 3, Major Task 1). As the investigators remain blinded to allocation of treatment assignment, it is not possible to know efficacy results until the end of the study. Safety is being continually monitored by collection of adverse events and their evaluation at a regularly held data safety monitoring committee meetings. Regular meetings with the medical monitor continue for review of all AEs and study procedures. No safety concerns have been identified and no changes in the study proposed.

Recruitment has been largely on track after a slightly delayed start due to delay from what was anticipated of regulatory approvals. There have been no impediments and treatment and data collection are proceeding without issues. No changes have been made in the statement of work and

only minor modifications of the protocol and informed consent have been made to align with the updated package insert (April 2016) for the study drug.

KEY RESEARCH ACCOMPLISHMENTS:

There are no outcome data available to date. As this is a blinded clinical trial, scientific data relating to study objectives will not be available until all participants have concluded the study, data cleaned and data base locked, and analyses completed.

CONCLUSION:

This project has not progressed to the point of being able to provide any conclusions in regard to the effect of these specific interventions on bone mass or bone quality in people after spinal cord injury. If benefit is shown, this intervention has the potential to reduce fracture incidence in people experiencing acute SCI.

PUBLICATIONS, ABSTRACTS AND PRESENTATIONS:

None.

INVENTIONS, PATENTS AND LICENSES:

None.

REPORTABLE OUTCOMES:

None.

OTHER ACHIEVEMENTS:

None.

REFERENCES:

None.

APPENDICES:

None.

Prevention of Bone Loss after Acute SCI by Zoledronic Acid: Durability, Effect on Bone Strength and Use of Biomarkers to Guide Therapy

Proposal Log Number SC130125; Award # W81XWH-14-2-0193; HRPO Log A-18350

PI: Dr. Thomas J. Schnitzer **Org:** Northwestern University Feinberg School of Medicine **Award Amount: $2,011,846**

Study/Product Aims

- Define timing and frequency of administration of zoledronic acid that will result in optimal prevention of bone loss after acute SCI.
- Evaluate the use of serum markers of bone metabolism to guide therapeutic decisions of timing and need for retreatment with zoledronic acid after acute SCI.
- Evaluate effects of zoledronic acid in mitigating loss of bone strength that occurs after acute SCI.

Approach

This is a 2 year, randomized, double-blind placebo-controlled study. Subjects will be randomized at baseline and again at 12 months to receive either zoledronic acid or placebo each time. Subject will be followed for 24 months with repeat DXA scans, CT scans, and serum bone markers.

IRB approval received at all sites. Recruitment and enrollment continues. Thirty subjects have been enrolled.

Timeline and Cost

Activities CY	14	15	16	17	18
Study Start-Up Activities					
Participant Enrollment					
Data Collection and Entry					
Data Analysis					
Estimated Budget ($K)	**$138K**	**$541K**	**$503K**	**$465K**	**$365K**

Updated: 27 October 2016

Goals/Milestones

CY14 Goals – Begin study start-up
- Obtain regulatory approval at all sites

CY15 Goal – Complete start-up, Begin recruitment and enrollment
- Enroll 25-30 subjects into study

CY16 Goal – Continue recruitment and enrollment
- Enroll 25-30 subjects into study

CY17 Goal – Complete subject enrollment

CY18 Goal – Complete data collection and data analysis
- Final study report

Comments/Challenges/Issues/Concerns
- Delayed HRPO approval delayed projected timelines, altered CY15 goal to 20-25 subjects
- Enrollment continues but remains slightly slower than planned
- Under budget to allow for longer recruitment period if needed

Budget Expenditure to Date (September, 2016)

Projected Expenditure: $1,085,212

Actual Expenditure: $570,453 (subcontract invoices outstanding)